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(54) Title: NOVEL DIPEPTIDYL PEPTIDASE IV INHIBITORS; PROCESSES FOR THEIR PREPARATION AND COMPOSITIONS THEREOF

(57) Abstract: The present invention relates to novel dipeptidyl peptidase IV (DPP-IV) inhibitors of the formula (I), and their analogs, isomers, pharmaceutical compositions and therapeutic uses, methods of making the same.

**NOVEL DIPEPTIDYL PEPTIDASE IV INHIBITORS;
PROCESSES FOR THEIR PREPARATION AND
COMPOSITIONS THEREOF**

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This application claims priority to Indian Provisional Application 1039/MUM/2003 filed October 3, 2003 and US Provisional Application 60/517,360 filed on November 4, 2003 which is incorporated herein by reference in their entireties.

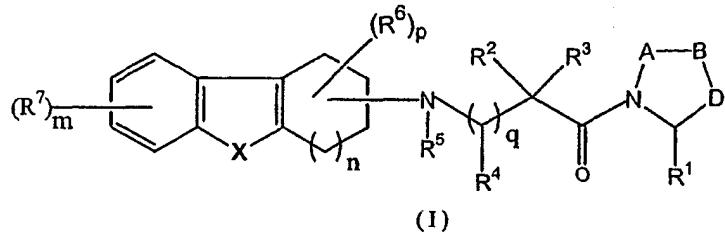
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FIELD OF THE INVENTION

The present invention relates to novel dipeptidyl peptidase IV (DPP-IV) inhibitors of the formula (I), and their analogs, isomers, pharmaceutical compositions and therapeutic uses.

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The novel compounds are of general formula (I)



wherein the ring formed by A, B, D, N and the carbon atom to which they are attached is saturated; or optionally contains one double bond; A, B and D may be same or different and are independently selected from the groups consisting of CH₂, CH, S, SO, SO₂, O, NH, N, N-Z, C=O, CF₂, CF, C-Z and CH-Z; wherein Z is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy or cyano;

wherein R¹ represents hydrogen or cyano; R², R³ and R⁴ may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or

unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, and -SR⁸; R⁸ is selected independently for each occurrence and represents hydrogen, nitro, hydroxy, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, R² and R³ taken together form oxo (=O); R² and R³ taken together form (=S); R² and R³ together with carbon atom to which both R² and R³ are attached form (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R² and R⁴ together with carbon atom to which both R² and R⁴ are attached form (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R⁵ represents hydrogen or substituted or unsubstituted alkyl; R⁶ and R⁷ may be same or different and are independently selected from the groups consisting of hydrogen, formyl, nitro, hydroxy, cyano, oxo (=O), acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ or when two R⁷ substituents are ortho to each other, may be joined to a form a saturated or unsaturated substituted or unsubstituted cyclic ring, which may optionally include up to two heteroatoms selected from O, NR⁹ or S(O)_r; X is oxygen, S(O)_r or NR⁹; wherein r is 0 – 2.

R⁹ represents hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted

arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_m-R⁸, -S(O)_n-NR⁸R⁸, -OR⁸, -SR⁸ and protecting groups, wherein m is 0 – 4; wherein n is 0 – 3; wherein p is 0 – 11; wherein q is 0 – 5; or an analog thereof, or a tautomeric form thereof, or a regioisomeric form thereof, or a stereoisomeric form thereof, or an enantiomeric form thereof, or a diastereomeric form thereof, or a polymorphic forms thereof, and/or a pharmaceutical compositions containing the same, or a salt, N-oxide, or solvate thereof with a pharmaceutically acceptable acid or base.

10

BACKGROUND OF THE INVENTION

Diabetes mellitus refers to a chronic metabolic disorder in which utilization of carbohydrates is impaired and that of lipids and proteins are enhanced. It is caused by an absolute or relative deficiency of insulin (the hormone which regulates the body's glucose utilization) and is characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test.

Persistent or uncontrolled hyperglycemia is associated with increased and premature morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Patients with diabetes mellitus are at increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension, nephropathy, neuropathy, and retinopathy. Therapeutic control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

Generally, there are two recognized forms of diabetes, known as type 1 and type 2. In type 1 diabetes, also known as insulin-dependent diabetes mellitus or "IDDM", patients produce little or no insulin. In type 2 diabetes, also known as non-insulin dependent diabetes mellitus or "NIDDM", patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects. NIDDM patients with elevated plasma insulin levels, however, often exhibit a developed resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, including: muscle, liver and adipose tissues. Thus, the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance. Insulin resistance is not primarily due to a

diminished number of insulin receptors but to a post-insulin receptor-binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue. In addition, insulin resistance results in insufficient glucose production and secretion in the liver.

5 Diabetes mellitus often develops in certain "at risk" populations. One such population is individuals with impaired glucose tolerance (IGT). The ordinary meaning of impaired glucose tolerance is a condition intermediate between normal glucose tolerance and NIDDM. IGT may be diagnosed by a test procedure that assesses an affected person's postprandial 10 glucose response. In this test, a measured amount of glucose is given to the patient and blood glucose levels are measured at regular intervals. These intervals occur every half hour for the first two hours and every hour thereafter. In a "normal" or non-IGT individual, glucose levels rise during the first two hours to a level less than 140 mg/dl and then drop rapidly. In an individual with IGT, the blood glucose levels are higher and the drop-off level occurs at a 15 slower rate. A high percentage of the IGT population is known to progress to NIDDM.

Insulin resistance is an abnormality of glucose disposal in tissues and organs, which 20 can be measured by various tests. For example, the euglycemic glucose clamp test, the intravenous glucose tolerance test, or by measuring the fasting insulin level. It is well known that there is an excellent correlation between the height of the fasting insulin level and the degree of insulin resistance. Therefore, one could use elevated fasting insulin levels as a 25 surrogate marker for insulin resistance for the purpose of identifying which NGT individuals have insulin resistance.

U.S. Patent No. 5,702,012 discloses that a certain patient population that tests normal according to the fasting and two hour postprandial plasma glucose tests(i.e. normal glucose 25 tolerance population) but exhibit insulin resistance using different tests, may progresses to NIDDM. This population is designated as having non-IGT (NIGT) or insulin resistant NIGT (IRNIGT). The reference further discloses that this population can be treated with the thiazolidinedione class of compounds.

It is important to distinguish between those individuals whose tests show normal 30 glucose tolerance and who are not insulin resistant on the one hand, and those who exhibit normal glucose tolerance with a certain degree of insulin resistance on the other hand.

The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and reductions in dietary

intake of calories may dramatically improve the diabetic condition, compliance with this treatment is very poor because of sedentary lifestyles and excess food consumption. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the pancreatic β -cells to secrete more insulin, 5 and/or by injection of insulin when sulphonylureas or meglitinide becomes ineffective, can results in insulin concentrations high enough to stimulate the very insulin-resistance tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide). In addition, the even higher plasma insulin levels may result in increased insulin resistance. The biguanide class of compounds 10 can increase insulin sensitivity resulting in some correction of hyperglycemia. However, two biguanides, phenformin and metformin, can also induce lactic acidosis and nausea/diarrhea. Metformin, which has fewer side effects than phenformin, is often prescribed for the treatment of type 2 diabetes.

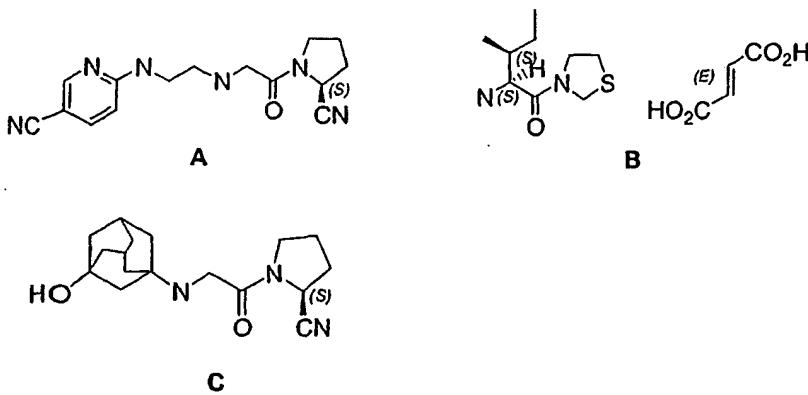
More recently, the glitazone class of compounds (i.e. 5-benzylthiazolidine-2,4-diones) 15 have been used to ameliorate many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue resulting in partial or complete correction of the elevated plasma glucose levels without occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. This PPAR-gamma agonism is 20 generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of Type II diabetes are agonists of the alpha, gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the PPAR agonists, such 25 as troglitazone.

Dipeptidyl peptidase-IV ("DPP-IV") has been implicated in the control of glucose metabolism because its substrates include the insulinotropic hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are active only in their intact forms and removal of their two N-terminal amino acids will inactivate them. 30 DPP-IV, a serine protease belonging to the group of post-proline/alanine cleaving amino-dipeptidases, specifically removes the two N-terminal amino acids from proteins such as GIP and GLP-1 which have proline or alanine in position 2. Although the physiological role of

DPP-IV has not been completely established, it is believed to play an important role in at least impaired fasting glucose (IFG) and diabetes.

In vivo administration of synthetic inhibitors of DPP-IV prevents N-terminal degradation of GLP-1 and GIP, which results in (I) higher plasma concentrations of these hormones; (II) increased insulin secretion; and (III) improved glucose tolerance. Thus, such DDP-IV inhibitors have been proposed for the treatment of patients with type II diabetes, a disease characterized by decreased glucose tolerance. In addition, since the body produces these hormones only when food is consumed, DPP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to 10 excessively low blood sugar (hypoglycemia). Inhibition of DPP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect associated with the use of insulin secretagogues.

Currently there are a few compounds under review in advanced stages of human clinical trials that have been shown to inhibit DPP-IV. For example, such compounds have 15 been disclosed in U.S. Patent No. 6,124,305, WO 98/19998, WO 03002530, WO 02083109, WO 00/34241, and WO 99138501. For example, Novartis "NVP-DPP-728" which has the formula A below, Probiot drug "P32/98" which has the formula B below and Novartis "NVP-LAF-237" which has the formula C below.



20 Although the above DPP-IV inhibitors have been described in the literature, all have limitations relating to their potency, stability, selectivity and/or toxicity. Therefore, there still exists a need for novel DPP-IV inhibitors, which are therapeutically useful in the treatment of medical conditions mediated by DPP-IV inhibition.

SUMMARY OF THE INVENTION

The present invention relates to novel DPP-IV inhibitors of the formula (I), and their analogs, isomers, pharmaceutical compositions and therapeutic uses. Such novel compounds are potent and selective inhibitors of DPP-IV, and are effective in treating conditions that may be regulated or normalized via inhibition of DPP-IV. The invention also concerns 5 pharmaceutical compositions comprising the novel compounds of formula (I), methods of inhibiting DPP-IV comprising administering to a subject in need thereof a therapeutically effective amount of said compound and processes for their preparation.

The present invention also relates to a method of using the DPP-IV inhibitors of formula (I) for the treatment of non-diabetic insulin resistant patients who do not have IGT. 10 Upon oral glucose tolerance testing, these subjects will have normal glucose tolerance as characterized by World Health Organization criteria. Treatment with these novel DPP-IV inhibitors of formula (I) may prevent or delay the onset of NIDDM.

In another aspect, the present invention relates administering to a subject in need thereof a therapeutically effective amount of a DPP-IV inhibitor of formula (I), wherein said subject is 15 neither in the state of NIDDM, nor in the state of IGT but who is insulin resistant with NGT in order to prevent or delay the onset of NIDDM or complications resulting therefrom. Since this subject group is insulin resistant, but does not have IGT, the group will be referred to as non-IGT (NIGT) or insulin resistant non-IGT (IRNIGT).

The DPP-IV inhibitory compounds of general formula (I) are useful for treating 20 diabetes, especially type II diabetes, as well as impaired glucose homeostasis, impaired glucose tolerance, infertility, polycystic ovary syndrome, growth disorders, frailty, arthritis, allograft rejection in transplantation, autoimmune diseases, AIDS, intestinal diseases, inflammatory bowel syndrome, anorexia nervosa, osteoporosis, hyperglycemia, dysmetabolic syndrome (syndrome X), diabetic complications, hyperinsulinemia, obesity, atherosclerosis 25 and related diseases, immunomodulatory diseases and chronic inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis.

The term 'alkyl' as used herein means a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having 30 from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like.

The term "Alkenyl" as used herein means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain

having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "Alkynyl" as used herein means a straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, butynyl and the like.

The term "Alkoxy" as used herein means an alkyl group as defined above attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are -OCH₃, -OC₂H₅ and the like.

10 The term "cycloalkyl" as used herein means a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl and norbornyl groups bridged cyclic group or spirobicyclic groups e.g. spiro (4,4) non-2-yl.

15 The term "cycloalkylalkyl" as used herein means a cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms directly attached to alkyl group which are then attached to the main structure at any carbon from alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobutylethyl, cyclopentylethyl, and the like.

20 The term "cycloalkenyl" as used herein means a cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms with at least one carbon- carbon double bond such as cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.

25 The term "aryl" as used herein means an aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl and the like.

The term "arylalkyl" as used herein means an aryl group as defined above directly bonded to an alkyl group as defined above. e.g., -CH₂C₆H₅, -C₂H₅C₆H₅ and the like.

30 The term "heterocyclic ring" as used herein means a stable 3- to 15 membered ring radical, which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various

oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated (i.e., heteroaromatic or heteroaryl aromatic). Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, 5 indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, 10 indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl 15 sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, isochromanyl and the like.

The term "heteroaryl" as used herein means a heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

20 The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroarylalkyl" as used herein means a heteroaryl ring radical as defined above directly bonded to alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

25 The term "heterocyclyl" as used herein means a heterocyclic ring radical as defined above. The heterocyclyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heterocyclylalkyl" as used herein means a heterocyclic ring radical as defined above directly bonded to alkyl group. The heterocyclylalkyl radical may be attached 30 to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term "cyclic ring" as used herein means a cyclic group containing 3-10 carbon atoms.

The term "halogen" as used herein means the radicals of fluorine, chlorine, bromine and iodine.

The substituents in the 'substituted alkyl', 'substituted alkoxy', 'substituted alkenyl', 'substituted alkynyl', 'substituted cycloalkyl', 'substituted cycloalkylalkyl', 'substituted 5 cyclocalkenyl', 'substituted arylalkyl', 'substituted aryl', 'substituted heterocyclic ring', 'substituted heteroaryl ring', 'substituted heteroarylalkyl', 'substituted heterocyclalkyl ring', 'substituted amino', 'substituted cyclic ring' and 'substituted carboxylic acid derivative' may be the same or different with one or more selected from the group such as hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio(=S), substituted or unsubstituted alkyl, 10 substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclalkyl ring, substituted or unsubstituted heteroarylalkyl, 15 substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, -COOR^x, -C(O)R^x, -C(S)R^x, -C(O)NR^xR^y, -C(O)ONR^xR^y, -NR^xCONR^yR^z, -N(R^x)SOR^y, -N(R^x)SO₂R^y, -(=N-N(R^x)R^y), -NR^xC(O)OR^y, -NR^xR^y, -NR^xC(O)R^y-, -NR^xC(S)R^y - NR^xC(S)NR^yR^z, -SONR^xR^y-, -SO₂NR^xR^y-, -OR^x, -OR^xC(O)NR^yR^z, -OR^xC(O)OR^y-, -OC(O)R^x, -OC(O)NR^xR^y, -R^xNR^yC(O)R^z, -R^xOR^y, -R^xC(O)OR^y, -R^xC(O)NR^yR^z, -20 R^xC(O)R^x, -R^xOC(O)R^y, -SR^x, -SOR^x, -SO₂R^x, -ONO₂, wherein R^x, R^y and R^z, chosen independently for each occurrence, in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted 25 aryl, substituted or unsubstituted heteroaryl, 'substituted heterocyclalkyl ring' substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring.

The term "drug delivery systems" as used herein means the technology utilized to present the drug to the desired body site for drug release and absorption.

30 The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms

of the state, disorder or condition, (II) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (III) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is
5 either statistically significant or at least perceptible to the patient or to the physician.

The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and
10 responsiveness of the mammal to be treated.

The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host means causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by local or by systemic administration of the active ingredient
15 to the host.

The term "subject" or "a patient" or "a host" as used herein refers to mammalian animals, preferably human.

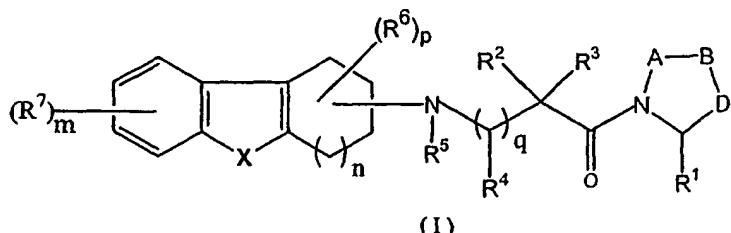
The term "pharmaceutically acceptable salt" as used herein includes salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; salts of organic bases such
20 as N,N'-diacetylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, thiamine, and the like; chiral bases like alkylphenylamine, glycinol, phenyl glycinol and the like, salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, serine,
25 and the like; quaternary ammonium salts of the compounds of invention with alkyl halides, alkyl sulphates like MeI, (Me)₂SO₄ and the like; non-natural amino acids such as D-isomers or substituted amino acids; guanidine, substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are,
30 sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like.

Pharmaceutically acceptable solvates may be hydrates or comprise other solvents of crystallization such as alcohols.

DETAILED DESCRIPTION OF THE INVENTION

5

The novel compounds are of general formula (I)



wherein the ring formed by A, B, D, N and the carbon atom to which they are attached is
 10 saturated; or optionally contains one double bond; A, B and D may be same or different and are independently selected from the groups consisting of CH₂, CH, S, SO, SO₂, O, NH, N, N-Z, C=O, CF₂, CF, C-Z and CH-Z; wherein Z is independently selected for each occurrence from the group consisting of hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy or cyano;
 15 wherein R¹ represents hydrogen or cyano; R², R³ and R⁴ may be same or different and are independently selected from the groups consisting of hydrogen, nitro, hydroxy, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or 20 unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, and -SR⁸; R⁸ is selected independently for each occurrence and
 25 represents hydrogen, nitro, hydroxy, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted

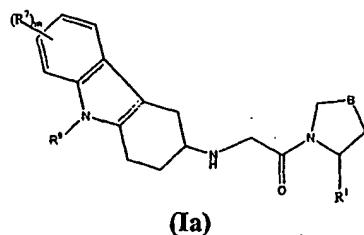
arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, R² and R³ taken together form oxo (=O); R² and R³ taken together form (=S); R² and R³ together with carbon atom to which both R² and R³ are attached form (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R² and R⁴ together with carbon atom to which both R² and R⁴ are attached form (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R⁵ represents hydrogen or substituted or unsubstituted alkyl; R⁶ and R⁷ may be same or different and are independently selected from the groups consisting of 5 hydrogen, formyl, nitro, hydroxy, cyano, oxo (=O), acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ or when two R⁷ 10 substituents are ortho to each other, may be joined to a form a saturated or unsaturated substituted or unsubstituted cyclic ring, which may optionally include up to two heteroatoms 15 selected from O, NR⁹ or S(O)_r; X is oxygen, S(O)_r or NR⁹; wherein r is 0 – 2.

R⁹ represents hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ and protecting groups, wherein m is 0 – 4; wherein n is 0 – 3; wherein p 25 is 0 – 11; wherein q is 0 – 5; or an analog thereof, or a tautomeric form thereof, or a regioisomeric form thereof, or a stereoisomeric form thereof, or an enantiomeric form thereof, or a diastereomeric form thereof, or a polymorphic forms thereof, and/or a pharmaceutical 30

compositions containing the same, or a salt, N-oxide, or solvate thereof with a pharmaceutically acceptable acid or base.

According to the present invention the preferred compounds of the general Formulas Ia, 5 Ib and Ic are also disclosed and have the general structure as given below;

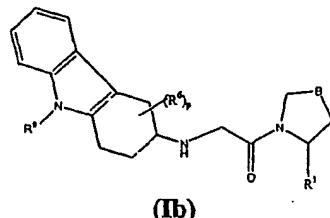
Preferred compounds of the general Formula Ia.



10 wherein m R^1 , R^7 and R^9 are the same as described above in the general formula I and B is selected from the group S or $-\text{CH}_2-$;

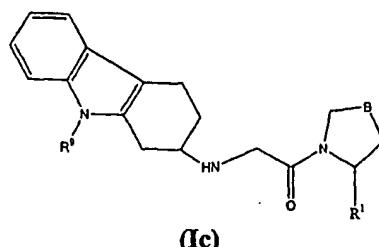
Preferred compounds of the general Formula Ib.

15



20 wherein p , R^1 , R^6 , R^9 are the same as described above in the general formula I and B is $-\text{CH}_2-$ group;

Preferred compounds of the general Formula Ic.



25 wherein R^1 , R^9 are the same as described above in the general formula I and B is $-\text{CH}_2-$ group;

Further preferred in Formulas Ia, Ib and Ic are where R¹ is hydrogen.

Further preferred in Formulas Ia, Ib and Ic are where R¹ is Cyano.

Further preferred in Formulas Ia, Ib and Ic are where R⁷ is -OR⁸ wherein R⁸ is methyl.

Further preferred in Formulas Ia, Ib and Ic are where R⁷ is halogen, preferably wherein the 5 halogen is selected from the group consisting of Cl and F.

Further preferred in Formulas Ia, Ib or Ic are where R⁷ is ethyl.

Further preferred in Formulas Ia, Ib or Ic are where R⁷ is phenyl.

Further preferred in Formulas Ia, Ib or Ic are where R⁷ is ethyl.

Further preferred in Formulas Ia, Ib or Ic are where R⁶ is methyl.

10 Further preferred in Formulas Ia, Ib or Ic are where R⁶ is hydroxymethyl.

Further preferred in Formulas Ia, Ib or Ic are where R⁹ is hydrogen.

Further preferred in Formulas Ia, Ib or Ic are where R⁹ is methyl.

Further preferred in Formulas Ia, Ib or Ic are where B is selected from the group consisting of 15 -CH₂- and -S-.

15 Further preferred in Formulas Ia, Ib or Ic are where m is 0 or 1.

Further preferred in Formulas Ia, Ib or Ic are where p is 1 or 2.

According to the present invention, by way of example only, representative preferred compounds of the formula (I) include:

- 1) 1-[2-(8-Methoxy,2,3,4,9-Tetrahydro-1*H*-3-carbazolylamino)acetyl]pyrrolidine-2(*S*)-20 carbonitrile or a pharmaceutically acceptable salt thereof.;
- 2) 1-{2-[(3*R*)2,3,4,9-Tetrahydro-1*H*-3-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.; and
- 3) 1-{2-[(3*S*)2,3,4,9-Tetrahydro-1*H*-3-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
- 25 4) 1-{2-[(2*RS*)-2,3,4,9-Tetrahydro-1*H*-2-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof
- 5) 1-{2-[(3*RS*)-3-Hydroxymethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}-pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof
- 6) 2-[(3*R*)-2,3,4,9-Tetrahydro-1*H*-3-carbazolylamino]-1-(1,3-thiazolan-3-yl)-1-ethanone30 or a pharmaceutically acceptable salt thereof
- 7) 1-{2-[(3*R*)-9-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

8) 1-{2-[(3*RS*)-3-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

9) 1-{2-[(3*RS*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

5 10) 1-{2-[(3*RS*)-6-Methoxy-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

11) 1-{2-[(3*RS*)-8-Ethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

12) 1-{2-[(3*RS*)-4,4,9-Trimethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}-pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

10 13) 1-{2-[(3*RS*)-8-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

14) 1-{2-[(3*RS*)-6-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

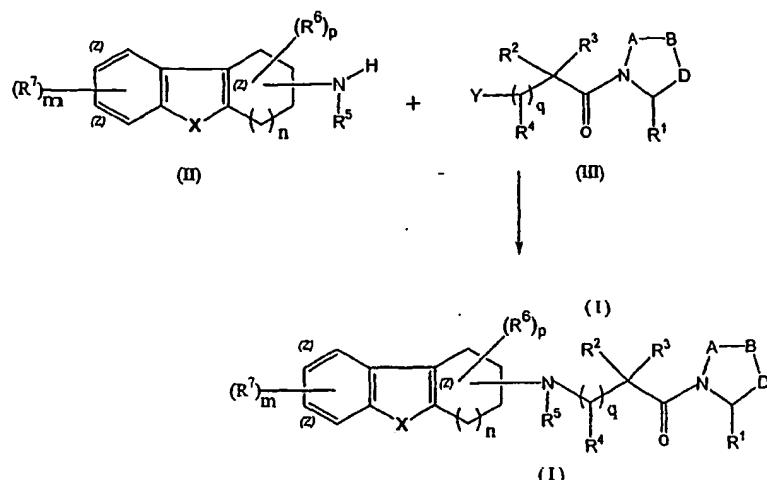
15 15) 1-{2-[(3*RS*)-8-Phenyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof

Another embodiment of the present invention provides processes of producing compounds of the formula (I) by the following steps as given in Scheme 1.

20

SCHEME 1: Preparation of compounds of the general formula I:

(a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of the formula (II),



wherein Y is a leaving group selected from the group consisting of bromine, chlorine, iodine, O-toulene sulphonyls and O-methyl sulphonyls, in the presence of additional bases such as a tertiary amine, a carbonate or a hydroxide;

5. (b) Said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;

(c) Said coupling occurring for between about 2 hrs to about 7 days; and

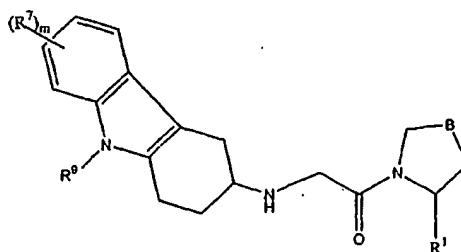
(d) Isolating the resulting compound of the formula (I).

The compounds of the formula (III) can be prepared by methods found in the literature. Starting amines of the general formula (II) can be prepared by methods found in the literature.

Similarly the preferred compounds of general formula Ia, Ib or Ic can be prepared as per the schemes 1a, 1b or 1c respectively as given below

SCHEME 1a: Preparation of compounds of the general formula Ia:

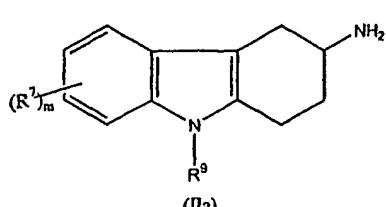
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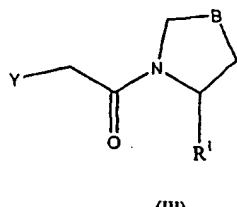
wherein R¹, R⁷ R⁹, m are the same as described above in the general formula I and B is selected from the group S or -CH₂;

which comprises the step of:

(a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of formula (IIa):



5



wherein Y is a leaving group, in an inert solvent in the presence of a base.

(b) said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;

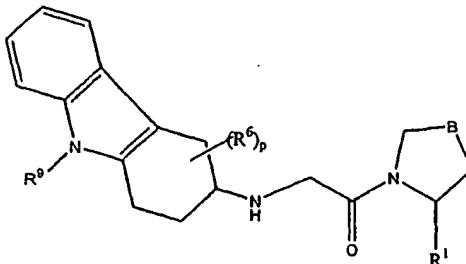
10 (c) said coupling occurring for between about 2 hrs to about 7 days; and

(d) isolating the resulting compound of the formula (Ia).

The compounds of the formula (III) can be prepared by methods found in the literature. Starting amines of the general formula (IIa) can be prepared by methods found in the literature.

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SCHEME 1b: Preparation of compounds of the general formula Ib:



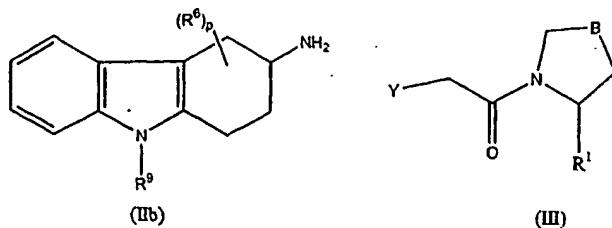
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wherein R¹, R⁶, R⁹, p are the same as described above in the general formula I and B is -CH₂- group;

which comprises the step of:

(a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of

25 an amine compound of formula (IIb):



wherein Y is a leaving group, in an inert solvent in the presence of a base.

(b) said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;

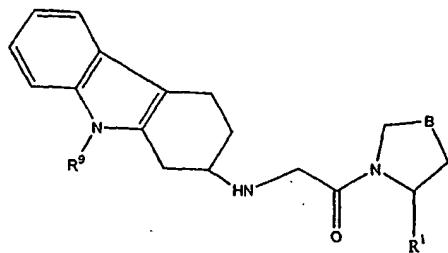
5 (c) said coupling occurring for between about 2 hrs to about 7 days; and

(d) isolating the resulting compound of the formula (Ib).

The compounds of the formula (III) can be prepared by methods found in the literature. Starting amines of the general formula (IIIb) can be prepared by methods found in the literature.

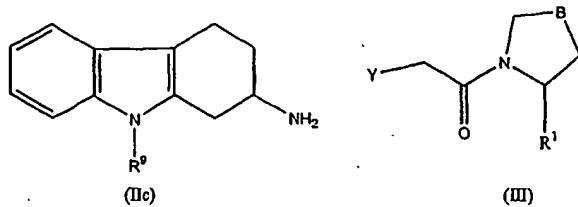
SCHEME 1c: Preparation of compounds of the general formula Ic:

15



wherein R^1, R^9 are the same as described above in the general formula I and B is –
20 CH_2 - group;
which comprises the step of:

(a) Coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of formula (IIC):



wherein Y is a leaving group, in an inert solvent in the presence of a base.

(b) Said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;

5 (c) Said coupling occurring for between about 2 hrs to about 7 days; and

(d) Isolating the resulting compound of the formula (Ic).

The compounds of the formula (III) can be prepared by methods found in the literature. Starting amines of the general formula (IIc) can be prepared by methods found in 10 the literature.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuum and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

15 In another embodiment, a pharmaceutically acceptable salt can be made using methods known to those skilled in the art. Salts are obtained by dissolving the free compound in a suitable solvent, e.g. in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts 20 are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification or by acidifying into the free compounds, which, in turn can be converted into salts.

The ethereal solvents used in the above described processes for the preparation of compounds of the formula (I) are selected from diethyl ether, 1,2-dimethoxyethane, 25 tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent, which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like. The aromatic solvents, which may be employed may be selected from benzene and toluene. The alcoholic solvents, which may be employed may be

selected from methanol, ethanol, n-propanol, isopropanol, tert-butanol and the like. The aprotic solvents, which may be employed may be selected from N, N-dimethylformamide, dimethyl sulfoxide and the like.

In yet another embodiment, compounds of the present invention may be purified by 5 using techniques such as (I) crystallization with solvents such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, ethanol, isopropanol, water or their combinations; or (II) column chromatography using alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

10 The present invention also provides, various polymorphs of a compound of general formula (I) prepared by crystallization. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs of a compound of general formula (I) may also be prepared via heating or 15 melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

20 The present invention further provides novel heterocyclic compounds, analogs thereof, or tautomeric forms thereof, or regioisomeric forms thereof, or stereoisomeric forms thereof, or enantiomeric forms thereof, or diastereomeric forms thereof, or polymorphic forms thereof, and/or a pharmaceutical compositions containing the same, or a salt, N-oxide, or solvate thereof with a pharmaceutically acceptable acid or base.

25 The present invention also provides pharmaceutical compositions, containing compounds of general formula (I) as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their enantiomers, their diasteromers, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

30 It will be appreciated that some of the compounds of general formula (I) defined above according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in the compounds of general formula (I) can give rise to stereoisomers and in each case the invention is to be understood to

extend to all such stereoisomers, including enantiomers and diastereomers and their mixtures, including racemic mixtures. The invention may also contain E and Z geometrical isomers wherever possible in the compounds of general formula (I), which includes the single isomer or mixture of both the isomers.

5 The acid addition salts of the present invention may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of
10 Pharmaceutical Science, 66, 2 (1977).

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one compound of the invention
15 which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

20 Pharmaceutical compositions containing a compound of the invention of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy, 19th Supp. Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

25 Typical compositions include a compound of the invention which inhibits the enzymatic activity of DPP-IV or a pharmaceutically acceptable basic addition salt or prodrug or hydrate thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols,

polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

15 The route of administration may be any route, which effectively transports the active compound of the invention which inhibits the enzymatic activity of DPP-IV to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral, e.g., rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

20 If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

25 For nasal administration, the preparation may contain a compound of the invention, which inhibits the enzymatic activity of DPP-IV, dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g., propylene glycol, surfactants, absorption enhancers, such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

30 For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, cornstarch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

5 A typical tablet that may be prepared by conventional tabletting techniques may contain: 1 Core: Active compound (as free compound or salt thereof) 250 mg Colloidal silicon dioxide (Aerosil®) 1.5 mg Cellulose, microcryst. (Avicel®) 70 mg Modified cellulose gum (Ac-Di-Sol®) 7.5 mg Magnesium stearate Ad. Coating: HPMC approx. 9 mg *Mywacett 9-40 T approx. 0.9 mg *Acylated monoglyceride used as plasticizer for film coating.

10 Where the term compound of Formula I is used, it is understood that this also encompasses subgeneric formulas IV and V.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of a condition that may be regulated or normalized via inhibition of DPP-IV.

15 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of a metabolic disorders.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for blood glucose lowering.

20 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of type II diabetes.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of 25 impaired glucose tolerance (IGT).

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of impaired fasting glucose (IFG).

30 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the prevention of hyperglycemia.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for delaying the progression of impaired glucose tolerance (IGT) to type II diabetes.

5 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for delaying the progression of non-insulin requiring type II diabetes to insulin requiring type II diabetes.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for increasing the number and/or the size of beta cells in a subject.

10 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of beta cell degeneration, in particular apoptosis of beta cells.

15 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of disorders of food intake.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of obesity.

20 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for appetite regulation or induction of satiety.

A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of dyslipidemia.

25 A further aspect of the present invention is the use of a compound of formula (I) as a pharmaceutical composition in a therapeutically effective amount for the treatment of functional dyspepsia, in particular irritable bowel syndrome.

A further aspect of the present invention is a method for the manufacture of a medicament or a pharmaceutical composition comprising admixing a compound of the invention and a pharmaceutically acceptable carrier or excipient.

30 The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of the various diseases as mentioned above, e.g., type II diabetes, IGT, IFG, obesity, appetite regulation or as a blood glucose lowering agent, and especially type II diabetes. Such

mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg, preferably from about 5 0.1 to about 500 mg, per day may be used. A most preferable dosage is about 0.5 mg to about 250 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and 10 the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration 15 comprise from about 0.05 mg to about 1000 mg, preferably from about 0.5 mg to about 250 mg of the compounds admixed with a pharmaceutically acceptable carrier or diluent.

The invention also encompasses prodrugs of a compound of the invention, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of a 20 compound of the invention, which are readily convertible in vivo into a compound of the invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

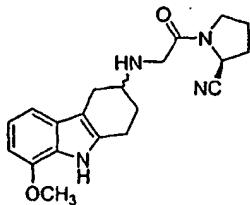
The invention also encompasses active metabolites of a compound of the invention.

25 **EXAMPLES**

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the claims.

30 **Example 1**

1-{2-[(3RS)-8-Methoxy-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine -
2(S)-carbonitrile



Step A: (3RS)-8-Methoxy-2,3,4,9-tetrahydro-1H-3-carbazolamine: This intermediate was prepared from 4-(N-BOC-amino)cyclohexanone and 2-methoxyphenyl hydrazine using a literature procedure (US Patent 4,988,820).

5 **Step B:** (2S)-1-(2-Chloroacetyl)pyrrolidine-2-carbonitrile: This intermediate was prepared from L-(-)-proline using a literature procedure (*J. Med. Chem.*, 2003, 46, 2774-2789).

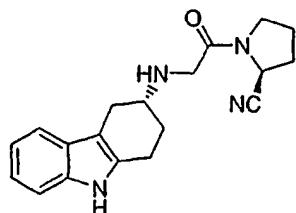
Step C: A solution of intermediate from step B (0.151 g, 0.875 mmol) in dry THF (5 ml) was added drop-wise to a cooled (-10 °C) and stirred mixture of the amine from Step A (0.378 g, 1.748 mmol) and K₂CO₃ (0.361 g, 2.615 mmol) in dry THF (5 ml) under nitrogen

10 atmosphere. The temperature of the reaction mixture was slowly raised to RT and maintained at RT for 20 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue obtained was purified on a neutral alumina column using 3 % methanol in dichloromethane to give 0.130 g (42 %) of the compound as a light brown solid; ¹H NMR (CDCl₃, 300 MHz) δ 1.7-1.9 (m, 4H), 2.08-2.33 (m, 4H), 2.46-2.6 (m, 1H), 2.78-2.9 (m, 2H), 2.96-3.1 (m, 2H), 3.4-3.72 (m, 3H), 3.94 (s, 3H), 4.76-4.8 (s, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.69-7.1 (m, 2H), 7.96 (b, 1H); IR (KBr) 3322, 2923, 2850, 1656, 1573, 1426, 1257, 1192, 1099, 777, 753, 730 cm⁻¹; MS (m/z): 353 (M+H).

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Example 2

20 1-{2-[(3R)-2,3,4,9-Tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile

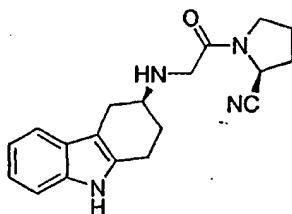


25 **Step A:** (3R)-2,3,4,9-Tetrahydro-1H-3-carbazolamine: This intermediate was synthesized in chiral form according to the procedure of Boshagen et al., US Patent 4,988,820.

Step B: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step A (1.0 g, 5.38 mmol) and (2S)-1-(2-chloroacetyl)-2-pyrrolidine carbonitrile (0.619 g, 3.59 mmol) to give 0.578 g (50 %) of the product as light brown solid; ¹H NMR (CDCl₃, 300 MHz) δ 1.8-2.34 (m, 7H), 2.5-2.6 (m, 1H), 2.79-2.85 (m, 2H), 3.0-3.1 (m, 2H), 5 3.4-3.7 (m, 4H), 4.76-4.8 (m, 1H), 7.04-7.15 (m, 2H), 7.24-7.26 (d embedded in solvent peak, 1H), 7.44 (d, *J* = 4.2 Hz, 1H), 7.8 (b, 1H). IR (KBr) 3274, 2836, 1659, 1428, 1313, 739 cm⁻¹.

10 Example 3

1-[(3S)-2,3,4,9-Tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile



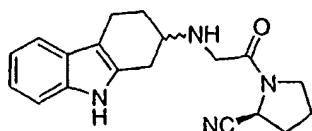
Step A: (3S)-2,3,4,9-Tetrahydro-1H-3-carbazolamine: This compound was synthesized according to a literature procedure (Boshagen et al., US Patent 4,988,820)

Step B: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step A and (2S)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give the compound as a light brown solid; ¹H NMR (CDCl₃, 300 MHz) δ 1.76-1.93 (m, 3H), 2.1-2.35 (m, 4H), 2.5-2.6 (m, 1H), 2.79-2.85 (m, 2H), 3.0-3.1 (m, 2H), 3.4-3.7 (m, 4H), 4.76-4.8 (m, 1H), 7.04-7.15 (m, 2H), 7.24-7.26 (1H, embedded in solvent peak), 7.44 (d, *J* = 4.2 Hz, 1H), 7.8 (b, 1H); IR (KBr): 3396, 2923, 1652, 1418, 1327, 1155, 744 cm⁻¹.

20

Example 4

1-[(2RS)-2,3,4,9-Tetrahydro-1H-2-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile



25 Step A: 2,3,4,9-Tetrahydro-1H-2-carbazolone: This compound was prepared according to a literature procedure (*J. Org. Chem.* 1973, 38, 2729)

Step B: (2RS)-2,3,4,9-Tetrahydro-1*H*-2-carbazolamine: The compound was synthesized by the reductive amination of 2,3,4,9-tetrahydro-1*H*-2-carbazolone (Step A) according to the procedure described by M. Barkley et al. in *J. Am. Chem. Soc.* 1995, 117, 348.

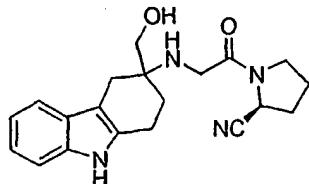
1 ¹HNMR (CDCl₃, 300 MHz) δ 1.60 (b, 2H), 1.68-1.80 (m, 1H), 2.10-2.11 (m, 1H), 2.51-2.59 (m, 1H), 2.68-2.92 (m, 2H), 3.01 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.32-3.42 (m, 1H), 7.05-7.15 (m, 2H), 7.28 (dd, *J* = 6.3, 1.2 Hz, 1H), 7.46 (dd, *J* = 6.3, 1.2 Hz, 1H), 7.75 (b, 1H).

5 **Step C:** The coupling reaction was carried out as described in Example 1, step C using the amine from Step B and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile as described in example 1, Step C to give the compound as a light brown solid; ¹HNMR (CD₃OD, 300 MHz) δ 1.65-1.91 (m, 1H), 1.95-2.40 (m, 5H), 2.54-3.18 (m, 5H), 3.45-3.55 (m, 1H), 3.54 (s, 2H), 3.57-3.72 (m, 1H), 4.75-4.81 (m, 1H), 6.89-7.02 (m + b, 3H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.80 (b, 1H). IR (KBr) 3295, 2925, 2852, 2242, 1659, 1418, 1314, 1140, 747 cm⁻¹.

15

Example 5

1-[2-[(3*RS*)-3-Hydroxymethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl]-pyrrolidine-2(*S*)-carbonitrile



Step A: (3*RS*)-3-Amino-2,3,4,9-tetrahydro-1*H*-3-carbazolecarboxylic acid: This compound was synthesized according to the procedure described by Y. Maki et al in *Chem. Pharm. Bull.* 1973, 21, 2460.

20 **Step B:** (3*RS*)-3-Amino-2,3,4,9-tetrahydro-1*H*-3-carbazolylmethanol: Lithium aluminum hydride (0.131 g, 3.47 mmol) was added to the suspension of 3-amino-2,3,4,9-tetrahydro-1*H*-3-carbazolecarboxylic acid (0.1 g, 0.43 mmol) in dry THF (5 ml) under N₂ atmosphere. 25 Reaction mixture was then refluxed for 15 h. The mixture was cooled to RT and quenched with saturated Na₂SO₄ solution. The mixture was filtered and the filtrate was evaporated under reduced pressure to give 0.88 g (93 %) of the alcohol as a pale yellow solid; ¹H NMR (CDCl₃, 300 MHz) δ 1.81 (b, 3H), 1.83-1.90 (m, 2H), 2.64-2.76 (m, 2H), 2.78-2.85 (m, 2H),

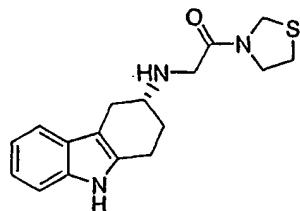
3.52 (s, 2H), 7.05-7.17 (m, 2H), 7.30 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.43 (d, $J = 7.2$ Hz, 1H), 7.80 (b, 1H).

Step C: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step B and (2S)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give the 5 compound as a light brown solid; 1 H NMR (CDCl₃, 300 MHz), (2H), 1.91-2.01 (m, 2H), 2.15-2.40 (m, 4H), 2.60-2.85 (m, 4H), 3.30-3.75 (m, 6H), 4.55-4.80 (m, 1H), 7.04-7.16 (m, 2H), 7.29 (d, $J = 7.2$ Hz, 1H), 7.42 (d, $J = 7.2$ Hz, 1H), 7.83 (b, 1H); IR (CCl₄): 3389, 3079, 2919, 1655, 1444, 1365, 1256, 1106, 1033, 928, 783, 698 cm⁻¹.

10

Example 6

2-[(3R)-2,3,4,9-Tetrahydro-1H-3-carbazolylamino]-1-(1,3-thiazolan-3-yl)-1-ethanone

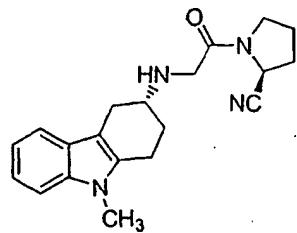


The carbazolamine from Example 2, Step A was coupled with 1-(chloroacetyl)-1,3-thiazolidine as described in Example 1, Step C to give the product as a light brown solid; 1 H NMR (CDCl₃, 300 MHz), (1H), 1.80-1.95 (m, 1H), 2.10-2.16 (m, 1H), 2.50-2.59 (m, 1H), 2.79-2.89 (m, 2H), 2.95-3.15 (m, 4H), 3.59 (d, $J = 7.8$ Hz, 2H), 3.73 (t, $J = 6.3$ Hz, 1H), 3.88 (t, $J = 6.3$ Hz, 1H), 4.49 (s, 1H), 4.62 (s, 1H), 7.04-7.15 (m, 2H), 7.27 (d, $J = 5.7$ Hz, 1H), 7.44 (d, $J = 7.8$ Hz, 1H), 7.75 (b, 1H); IR (KBr) 3396, 3292, 2922, 2840, 1643, 1429, 1327, 1143, 1009, 743 cm⁻¹.

20

Example 7

1-{2-[(3R)-9-Methyl-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile



Step A: *N3,N3-Dibenzyl-(3R)-2,3,4,9-tetrahydro-1H-3-carbazolamine:* To the solution of 2,3,4,9-tetrahydro-1*H*-3(*R*)-carbazolamine (0.29 g, 1.56 mmol) in THF (5 ml) was added K₂CO₃ (0.646 g, 4.68 mmol) followed by addition of benzyl bromide (0.56 g, 3.27 mmol) in THF (2 ml). The reaction mixture was stirred for 18 h at RT. It was then filtered, evaporated and concentrated in vacuo. The residue obtained was purified by recrystallization from dichloromethane-petroleum ether to give 0.32 g (57 %) of the compound as off-white solid; ¹H NMR (CDCl₃, 300 MHz): δ1.82-1.98 (m, 1H), 2.18-2.30 (m, 1H), 2.62-3.38 (m, 5H), 3.72 (d, *J* = 14.1 Hz, 2H), 3.82 (d, *J* = 14.1 Hz, 2H), 7.08-7.45 (m, 19H), 7.85 (b, 1H).

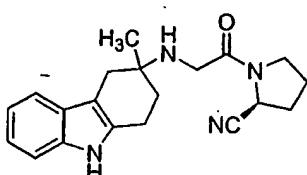
Step B: *N3,N3-Dibenyal-(3R)-9-methyl-2,3,4,9-tetrahydro-1H-3-carbazolamine:* *N3,N3-dibenzyl-(3R)-2,3,4,9-tetrahydro-1H-3-carbazolamine* (0.312 g, 0.927 mmol) in DMF (3 ml) was added to a stirred suspension of 60 % NaH (0.071 g, 1.85 mmol) in dry DMF (3 ml) under nitrogen. The mixture was stirred for 15 min. to result a dark brown solution. Methyl iodide (0.263 g, 1.85 mmol) was then added and further stirred for 30 min. Reaction mixture was poured on crushed ice and extracted with DCM (3 x 30 ml). The combined DCM extracts were washed successively with water (3 x 20 ml) and brine, dried over anhydrous Na₂SO₄ and concentrated under vacuum to yield 0.320 g (98 %) of the product as a viscous oil; ¹H NMR (CDCl₃, 300 MHz) δ1.84-2.00 (m, 1H), 2.22-2.32 (m, 1H), 2.60-3.18 (m, 5H), 3.56 (s, 3H), 3.73 (d, *J* = 14.1 Hz, 2H), 3.82 (d, *J* = 14.1 Hz, 2H), 7.00-7.32 (m, 9H), 7.42-7.49 (m, 5H).

Step C: *(3R)-9-Methyl-2,3,4,9-tetrahydro-1H-3-carbazolamine:* Methanolic HCl was added to the solution of step B intermediate (0.320 g, 0.913 mmol) in the mixture of methanol and chloroform (10 ml, 1:1) and the mixture was stirred at RT for 10 min. The solvents were evaporated under vacuum to yield a crystalline residue. The residue was dissolved in methanol (8 ml) and to this solution, was added ammonium formate (0.574 g, 9.0 mmol) and 10 % Pd-C (0.30 g). Reaction mixture was refluxed for 1 h, cooled to RT and filtered through a celite bed. The filtrate was evaporated and the residue was dissolved in 2*N* aqueous sulfuric acid by warming to 50 °C. The aqueous solution containing the product was washed with ethyl acetate (2 x 50 ml). The aqueous layer was cooled and basified with 2*N* sodium hydroxide solution. The precipitated compound was extracted with DCM (3 x 30 ml). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to give 0.150 g (82 %) of the compound as a viscous oil; ¹H NMR (CDCl₃, 300 MHz) δ1.50 (b, 2H), 1.75-1.88 (m, 1H), 2.04-2.13 (m, 1H), 2.45-2.56 (m, 1H); 2.72-2.92 (m, 2H), 3.05 (d, *J* = 15 Hz, 4.5 Hz, 1H), 3.22-3.35 (m, 1H), 3.62 (s, 3H), 7.04-7.10 (m, 1H), 7.13-7.19 (m, 1H); 7.25 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H).

Step D: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step C (as above) and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz): δ 1.73 (b, 1H), 1.79-1.98 (m, 1H), 2.10-2.40 (m, 5H), 2.51-2.68 (m, 1H), 2.70-2.95 (m, 2H), 2.98-3.12 (m, 2H), 3.42-5.52 (m, 1H), 3.53 (d, J = 5.4 Hz, 2H), 3.62 (s, 3H), 3.62-3.71 (m 1H), 4.75-4.85 (m, 1H), 7.04-7.09 (m, 1H), 7.12-7.18 (m, 1H), 7.25 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H). IR (neat): 3325, 2924, 2847, 1659, 1472, 1417, 1380, 1312, 1185, 1128, 1041, 743 cm^{-1} .

Example 8

10 1-{2-[(3*RS*)-3-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile



15 **Step A:** 4-(N-BOC-Amino)-4-methyl-1-cyclohexanone: This compound was prepared from 4-methyl-3-cyclohexene-1-ol according to a literature procedure (Lesher et al., US Patent 3,901,920)

20 **Step B:** (3*RS*)-*N*3-BOC-3-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: Phenyl hydrazine hydrochloride (0.195 g, 0.88 mmol) was added to a stirred solution of step A intermediate (0.20 g, 0.88 mmol) in ethanol (8 ml) and the reaction mixture was heated at 70 °C for 1 h. Ethanol was evaporated under vacuum to give a residue which was dissolved in ethyl acetate (100 ml) and washed successively with 10 % hydrochloric acid, water and brine. The organic solution was dried (Na_2SO_4) and concentrated under vacuum to yield 0.18 g (68 %) of the product as a orange-brown solid; ^1H NMR (CDCl_3 , 300 MHz) δ 1.40 (s, 9H), 1.42-1.50 (m, 1H), 1.55 (s, 3H), 1.72-1.83 (m, 1H), 2.68-2.74 (m, 2H), 2.78 (s, 2H), 7.06-7.17 (m, 2H), 7.30 (dd, J = 6.9 Hz, 0.9 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.80 (b, 1H).

25 **Step C:** 3-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: Dry HCl gas was bubbled into the ice-cold solution of *N*3-BOC-3-methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine (0.180 g, 0.60 mmol) in ethyl acetate till saturation (10 min). The mixture was stirred at RT for 30 min. Ethyl acetate was removed under vacuum and the residue obtained was diluted with water and basified with 2*N* sodium hydroxide solution. The solution was extracted with dichloromethane (3 x 25 ml). The combined organic extracts were washed with brine (25 ml)

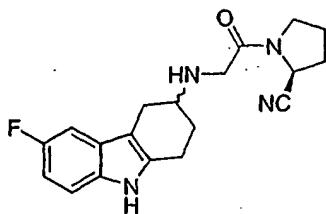
and dried (Na_2SO_4). The solvent was evaporated to give 0.130 g (98 %) of the free amine as a brown solid; ^1H NMR (CDCl_3 , 300 MHz) δ 1.29 (s, 3H), 1.52 (b, 2H), 1.84 (t, J = 6.3 Hz, 2H), 2.61-2.92 (m, 4H), 7.05-7.16 (m, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.77 (b, 1H).

5 Step D: The coupling reaction was carried out as described in Example 1, step C using the amine from Step C and (2S)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz) δ 1.24 (s, 3H), 1.86 (b, 1H), 1.80-2.27 (m, 6H), 2.65-2.87 (m, 4H), 3.33-3.44 (m, 1H), 3.48 (d, J = 5.4 Hz, 2H), 3.55-3.64 (m, 1H), 4.60-4.86 (m, 1H), 7.03-7.14 (m, 2H), 7.27 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.88 (b, 1H); IR (KBr): 3398, 3053, 2958, 2921, 2850, 2241, 1657, 1413, 1327, 1262, 1188, 1161, 1098, 742 cm^{-1} .

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Example 9

15 1-{2-[(3RS)-6-Fluoro-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile



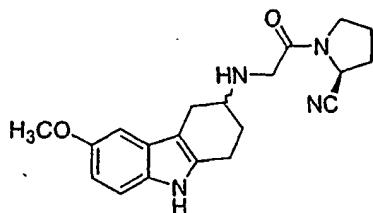
Step A: (3RS)-N3-BOC-6-Fluoro-2,3,4,9-tetrahydro-1H-3-carbazolamine: The compound was synthesized from 4-fluorophenylhydrazine and 4-(N-BOC-amino)cyclohexane-1-one as described in Example 8, Step B. ^1H NMR (CDCl_3 , 300 MHz) δ 1.46 (s, 9H), 1.90-1.98 (m, 1H), 2.05-2.18 (m, 1H), 2.54 (d, J = 15.3 Hz, 6.9 Hz, 1H), 2.79-2.88 (m, 2H), 3.04 (dd, J = 15.6 Hz, 5.4 Hz, 1H), 4.04-4.18 (m, 1H), 6.83-6.90 (m, 1H), 7.07 (dd, J = 9.3 Hz, 2.1 Hz, 1H), 7.18 (dd, J = 8.7, 4.5 Hz, 1H), 7.80 (b, 1H).

Step B: (3RS)-6-Fluoro-2,3,4,9-tetrahydro-1H-3-carbazolamine: The compound was synthesized from N3-BOC-6-fluoro-2,3,4,9-tetrahydro-1H-3-carbazolamine following the procedure described in Example 8, Step C. ^1H NMR (CDCl_3 , 300 MHz): δ 1.60 (b, 2H), 1.75-1.85 (m, 1H), 2.04-2.09 (m, 1H), 2.42 (dd, J = 15.3 Hz, 8.4 Hz, 1H), 2.82 (t, J = 6.3 Hz, 2H), 2.98 (dd, J = 15.3, 4.5 Hz, 1H), 3.26-3.40 (m, 1H), 6.85 (m, 1H), 7.08 (dd, J = 9.6, 2.4 Hz, 1H), 7.17 (dd, J = 8.7, 4.5 Hz, 1H), 7.77 (b, 1H).

Step C: The coupling reaction was carried out using the amine from Step B and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile as described in example 1, Step C to give of the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz) δ 1.70-2.00 (m + b, 2H), 2.04-2.33 (m, 5H), 2.42-2.51 (m, 1H), 2.78-2.80 (m, 2H), 2.91-3.12 (m, 2H), 3.41-3.51 (m, 1H), 5 3.53-3.56 (m, 2H), 3.61-3.70 (m, 1H), 4.74-4.79 (m, 1H), 6.81-6.88 (m, 1H), 7.08 (d, J = 9.9 Hz, 1H), 7.15-7.19 (m, 1H), 7.77 (b, 1H); IR (KBr) 3293, 2918, 2241, 1655, 1584, 1454, 1420, 1316, 1169, 1128, 914, 796 cm^{-1} .

Example 10

10 1-{(2*-(3RS)-6-Methoxy-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile*



Step A: (3RS)-*N*3-BOC-6-Methoxy-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized from 4-methoxyphenylhydrazine and 4-(*N*-BOC-amino)cyclohexane-1-one 15 as described in Example 8, Step B. ^1H NMR (CDCl_3 , 300 MHz): δ 1.45 (s, 9H), 1.80-2.04 (m, 1H), 2.05-2.18 (m, 1H), 2.56 (dd, J = 15.6 Hz, 6.9 Hz, 1H), 2.75-2.84 (m, 2H), 3.06 (dd, J = 15.0 Hz, 4.8 Hz, 1H), 3.85 (s, 3H), 4.05-4.18 (m, 1H), 4.71 (b, 1H), 6.78 (dd, J = 8.7, 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.67 (b, 1H).

Step B: 6-Methoxy-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized 20 from Step A intermediate by following the procedure described in Example 8, Step C. ^1H NMR (CDCl_3 , 300 MHz): δ 1.71-1.98 (m+b, 3H), 2.05-2.17 (m, 1H), 2.50 (dd, J = 15.0 Hz, 8.4 Hz, 1H), 2.81 (t, J = 6.3 Hz, 2H), 3.00 (dd, J = 15.0, 4.5 Hz, 1H), 3.27-3.88 (m, 1H), 3.85 (s, 3H), 6.78 (dd, J = 8.7, 2.4 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.65 (b, 1H)

25 Step C: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step B and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give of the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz): δ 2.05-2.45 (m, 5H), 1.71-1.98 (m, 1H), 2.56-2.78 (m, 1H), 2.81-2.92 (m, 2H), 2.95-3.18 (m, 1H), 3.20-3.80 (m, 5H),

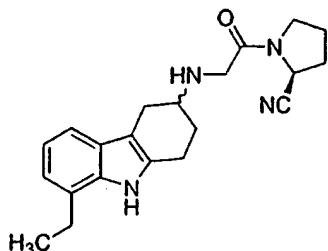
3.85*, 3.86* (s, 3H), 4.65-4.75 (m, 1H), 6.75-6.79 (m, 1H), 6.87-6.95 (m, 1H), 7.14-7.18 (m, 1H), 7.63 (b, 1H).

*diastereomeric protons

5

Example 11

1-{2-[(3RS)-8-Ethyl-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile



Step A: (3RS)-N3-BOC-8-Ethyl-2,3,4,9-tetrahydro-1H-3-carbazolamine: This intermediate was synthesized by reacting 2-ethylphenylhydrazine with 4-(N-BOC-amino)cyclohexane-1-one as described in Example 8, Step B. ¹H NMR (CDCl₃, 300 MHz): δ 1.35 (t, *J* = 7.8 Hz, 3H), 1.50 (s, 9H), 1.80-2.05 (m, 1H), 2.08-2.15 (m, 1H), 2.60 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.75-2.80 (m, 2H), 2.80 (q, *J* = 7.8 Hz, 2H), 3.08 (dd, *J* = 15.6, 4.8 Hz, 1H), 4.08-4.19 (m, 1H), 4.70 (b, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.72 (b, 1H).

Step B: (3RS)-8-Ethyl-2,3,4,9-tetrahydro-1H-3-carbazolamine: The compound was synthesized from Step A intermediate following the procedure described in Example 8, Step C. ¹H NMR (CDCl₃, 300 MHz): δ 1.35 (t, *J* = 7.8 Hz, 3H), 1.56 (b, 2H), 1.77-1.87 (m, 1H), 2.02-2.12 (m, 1H), 2.46 (m, 1H), 2.80-2.90 (m, 2H), 2.82 (q, *J* = 7.8 Hz, 2H), 3.00-3.07 (m, 1H), 3.26-3.35 (m, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 7.04 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.74 (b, 1H).

Step C: The coupling reaction was carried out as described in Example 1, step C using the amine from Step B and (2S)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give of the compound as a light brown solid; ¹H NMR (CDCl₃, 300 MHz) δ 1.32 (t, *J* = 7.8 Hz, 3H), 1.76 (b, 1H), 1.74-1.90 (m, 1H), 2.10-2.32 (m, 5H), 2.50-2.58 (m, 1H), 2.81 (q, *J* = 7.8 Hz, 2H), 2.78-2.90 (m, 2H), 3.00-3.15 (m, 2H), 3.44-3.55 (m, 1H), 3.56*, 3.57* (s, 2H), 3.60-3.70 (m, 1H), 4.72-4.89 (m, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.2

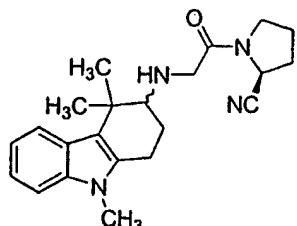
Hz, 1H), 7.70 (b, 1H); IR (neat): 3331, 2960, 2926, 2241, 1654, 1420, 1336, 1317, 1191, 1154, 749 cm⁻¹.

*diastereomeric protons

5

Example 12

1-{2-[(3RS)-4,4,9-Trimethyl-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}-pyrrolidine-2(S)-carbonitrile



Step A: 3,3-Ethylenedioxy-2,3,4,9-tetrahydrocarbazole: This intermediate was prepared
10 according to a literature procedure (Britten et al. *J. Chem. Soc. Perkin Trans- I* 1974, 1824).

Step B: 3,3-Ethylenedioxy-9-methyl-2,3,4,9-tetrahydro-1H-carbazole: This intermediate was prepared by *N*-methylation of Step A intermediate as described in Example 8, Step B. ¹H NMR (DMSO_d₆, 300 MHz) δ 1.98 (t, *J* = 6.3 Hz, 2H), 2.83-2.86 (s+t, 4H), 3.60 (s, 3H), 3.95 (s, 4H), 6.96 (t, *J* = 7.2 Hz, 1H), 7.03-7.09 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 2H).

15 Step C: 9-Methyl-2,3,4,9-tetrahydro-1H-3-carbazolone: 2*N* hydrochloric acid was added to the solution of 3,3-ethylenedioxy-9-methyl-2,3,4,9-tetrahydro-1H-carbazole (3.4 g, 13.97 mmol) in methanol (50 ml) and the mixture was refluxed for 30 min. Most of the methanol was evaporated under vacuum and the aqueous layer was extracted with DCM (3 x 50 ml). The combined organic extract was washed with brine and dried (Na₂SO₄). The solvent was 20 evaporated under vacuum to yield 2.74 g (98 %) of the compound as a brown solid; ¹H NMR (CDCl₃, 300 MHz) δ 2.83 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 3.68 (s, 3H), 7.09-7.14 (m, 1H), 7.20-7.31 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H).

Step D: 4,4,9-Trimethyl-2,3,4,9-tetrahydro-1H-3-carbazolone: Potassium *tert*-butoxide (2.73 g, 24.33 mmol) was added to the solution of 9-methyl-2,3,4,9-tetrahydro-1H-3-carbazolone (2.20 g, 11.06 mmol) in dry THF (20 ml) under N₂ at 0 °C. The mixture was stirred for 15 min and methyl iodide (3.45 g, 24.33 mmol) was added to the reaction mixture. The mixture was stirred at

RT for 30 min. and then quenched with ice cold water. The mixture was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with brine and dried over anhydrous Na₂SO₄. The residue obtained after evaporation of the solvent was chromatographed on neutral alumina using EtOAc-petroleum ether as eluent to yield 1.11 g (44 %) of the compound as off-white solid; ¹H NMR (DMSOD₆, 300 MHz) δ 1.48 (s, 6H), 2.80 (t, *J* = 6.3 Hz, 2H), 3.11 (t, *J* = 6.9 Hz, 2H), 3.63 (s, 3H), 6.97-7.02 (m, 1H), 7.08-7.13 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H).

Step E: *N*3-[(1*S*)-1-Phenylethyl]-4,4,9-trimethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The Step C intermediate (0.485 g, 2.13 mmol) and (1*S*)-1-phenylethylamine (0.28 g, 2.34 mmol) were refluxed in xylene overnight. The solvent was evaporated under reduced pressure and the residue obtained was taken up in dichloromethane (10 ml). The dichloromethane solution was added drop-wise to a stirred solution of tetra-*n*-butylammonium borohydride (0.55 g, 2.13 mmol) in DCM (10 mL) at -50 °C under N₂. Reaction mixture was warmed to RT over a period of 30 min. Reaction was quenched by the addition of methanol (0.24 ml) followed by careful addition of 2*N* H₂SO₄ (5 ml). Dichloromethane was evaporated and aqueous solution was washed with ethyl acetate. The aqueous layer was then basified with 2*N* NaOH solution and extracted with DCM (3 x 50 ml). The combined DCM layer was washed with water, brine and dried (Na₂SO₄). The solvent was evaporated under reduced pressure to yield 0.280 g (40 %) of the compound as brown semisolid; ¹H NMR (CDCl₃, 300 MHz): δ 1.58-1.68 (m, 1H), 1.88-1.99 (m, 1H), 2.52-2.78 (m, 4H), 3.57 (s, 3H), 3.94 (q, *J* = 6.3 Hz, 1H), 7.02-7.07 (m, 1H), 7.10-7.16 (m, 1H), 7.16-7.44 (m, 6H), 7.72 (d, *J* = 7.8 Hz, 1H).

Step F: (3*RS*)-4,4,9-Trimethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The Step D intermediate was debenzylated according to the procedure described in Example 8, Step C to give the product as an oil; ¹H NMR (CDCl₃, 300 MHz) δ 1.34 (s, 3H), 1.51 (s, 3H), 1.52 (b, 2H), 1.82-1.92 (m, 1H), 1.98-2.08 (m, 1H), 2.75-2.80 (m, 2H), 2.92 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.60 (s, 3H), 7.03-7.08 (m, 1H), 7.12-7.17 (m, 1H), 7.25 (d, *J* = 6.0 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H).

Step G: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step F and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give the compound as a light brown solid. ¹H NMR (CDCl₃, 300 MHz) δ 1.40 (s, 3H), 1.59 (s, 3H), 1.68 (b, 1H),

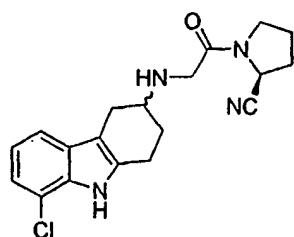
1.76-190 (m, 1H), 2.07-2.32 (m, 4H), 2.60-2.84 (m, 3H), 3.44-3.68 (m, 2H), 3.59 (s, 3H), 4.78-4.80*, 4.95-4.98* (m, 1H), 7.02-7.07 (m, 1H), 7.11-7.16 (m, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H); IR (neat) 3434, 2930, 1660, 1469, 1413, 1305, 1191, 1155, 839, 740 cm^{-1} .

5 *diastereomeric protons

Example 13

1-{(3*RS*)-8-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino}acetyl}pyrrolidine-2(*S*)-carbonitrile

1.0



Step A: *N*3-BOC-8-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was prepared from 2-chlorophenylhydrazine and 4-(*N*-BOC-amino)cyclohexan-1-one as described in Example 8, Step B. ^1H NMR (CDCl_3 , 300 MHz) δ 1.53 (s, 9H), 1.82-1.98 (m, 1H), 2.10-2.22 (m, 1H), 2.58 (dd, J = 16.8, 6.9 Hz, 1H), 2.80-2.90 (m, 2H), 3.08 (dd, J = 15.6, 5.4 Hz, 1H), 4.06-4.18 (m, 1H), 4.68 (b, 1H), 7.01 (t, J = 7.8 Hz, 1H), 7.13 (dd, J = 7.8, 1.2 Hz 1H), 7.33 (d, J = 7.8 Hz, 1H), 8.00 (b, 1H).

Step B: (3*RS*)-8-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized from *N*3-BOC-8-chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolamine following the procedure described in Example 8, Step C. ^1H NMR (CDCl_3 , 300 MHz) δ 1.78-1.88 (m, 1H), 2.01-2.15 (m, 1H), 2.48 (dd, J = 14.7, 7.8 Hz, 1H), 2.80-2.88 (m, 2H), 3.03 (dd, J = 15.6, 5.1 Hz, 1H), 3.15-3.25 (m, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 8.02 (b, 1H).

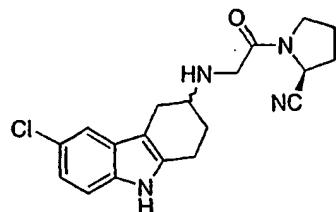
Step C: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step B and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give of the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz) δ 1.80-1.98 (m, 1H), 1.82 (b, 1H), 2.01-2.42 (m,

5H), 2.48-2.61 (m, 1H), 2.80-2.98 (m, 2H), 2.99-3.18 (m, 2H), 3.40-3.55 (m, 1H), 3.56 (s, 2H), 3.57-3.80 (m, 1H), 4.61-4.82 (m, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 8.02 (b, 1H); IR (KBr) 3299, 3029, 2926, 2856, 2239, 1713, 1650, 1541, 1420, 1327, 775, 700 cm^{-1} .

5

Example 14

10-*{2-[(3RS)-6-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile*



10

Step A: (3RS)-N3-BOC-6-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized by from 4-chlorophenylhydrazine and 4-(*N*-BOC-amino)cyclohexan-1-one as described in Example 8, Step B. ^1H NMR (CDCl_3 , 300 MHz) δ 1.44,* 1.46* (s, 9H), 1.53-1.70 (m, 1H), 1.89-1.98 (m, 1H), 2.53 (dd, J = 15.3, 6.9 Hz, 1H), 2.78-2.88 (m, 2H), 3.04 (dd, J = 15.6, 4.8 Hz, 1H), 4.05-4.18 (m, 1H), 4.68 (b, 1H), 7.07 (dd, J = 8.7, 1.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.83 (b, 1H)

15 *Rotameric protons

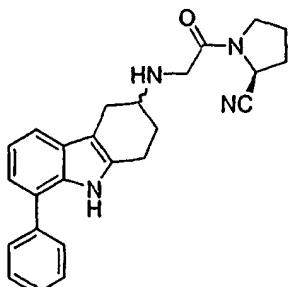
Step B: (3RS)-6-Chloro-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized from Step A intermediate as described in Example 8, Step C. ^1H NMR (CDCl_3 , 300 MHz) δ 1.62 (b, 2H), 1.72-1.79 (m, 1H), 1.98-2.10 (m, 1H), 2.42 (dd, J = 14.4 Hz, 8.1 Hz, 1H), 2.82 (t, J = 6.0 Hz, 2H), 2.97 (dd, J = 14.7, 4.5 Hz, 1H), 3.25-3.88 (m, 1H), 7.06 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.87 (b, 1H).

Step C: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step D and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give of the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz): δ 1.71-1.98 (m, 1H), 2.01-2.41 (m, 5H), 2.52-

2.75 (m, 1H), 2.80-2.91 (m, 2H), 2.93-3.05 (m, 1H), 3.10-3.80 (m, 5H), 4.65-4.74 (m, 1H), 7.04-7.08 (m, 1H), 7.14 (dd, J = 9.0, 1.8 Hz, 1H), 7.38-7.41 (m, 1H), 7.83 (b, 1H).

Example 15

5 **1-{2-[(3RS)-8-Phenyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile**



Step A: (3RS)-N3-BOC-8-Phenyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized from 2-phenylphenylhydrazine and 4-(*N*-BOC-amino)cyclohexan-1-one as described in Example 8, Step B. ^1H NMR (CDCl_3 , 300 MHz): δ 1.44,* 1.46* (s, 9H), 1.91-2.02 (m, 1H), 2.07-2.19 (m, 1H), 2.63 (dd, J = 15.6, 6.6 Hz, 1H), 2.78-2.85 (m, 2H), 3.12 (dd, J = 15.0 Hz, 4.5 Hz, 1H), 4.08-4.20 (m, 1H), 4.71 (b, 1H), 7.15-7.20 (m, 2H), 7.37-7.53 (m, 4H), 7.60-7.64 (m, 2H), 8.00 (b, 1H) *Rotameric protons

Step B: (3RS)-8-Phenyl-2,3,4,9-tetrahydro-1*H*-3-carbazolamine: The compound was synthesized from Step A intermediate by following the procedure described in Example 8

Step C: The coupling reaction was carried out as described in Example 1, Step C using the amine from Step B and (2*S*)-1-(2-chloroacetyl)-2-pyrrolidinecarbonitrile to give the compound as a light brown solid; ^1H NMR (CDCl_3 , 300 MHz) δ 1.80-1.98 (m, 1H), 2.10-2.40 (m, 5H), 2.52-2.68 (m, 1H), 2.78-2.90 (m, 2H), 3.01-3.18 (m, 2H), 3.41-3.56 (m, 1H), 3.57 (d, J = 3.6 Hz, 2H), 3.60-3.78 (m, 2H), 4.65-4.77 (m, 1H), 7.13-7.20 (m, 2H), 7.36-7.53 (m, 4H), 7.59-7.64 (m, 2H), 7.98 (b, 1H).

PROTOCOL FOR THE DPP-IV ASSAY

DPP-IV inhibition measurement in vitro: DPP-IV activity was determined by the cleavage rate of 7-amino-4-methyl coumarin (AMC) from synthetic substrate Glycyl-Prolyl-AMC. In brief, the assay was conducted by adding 10 ng of human recombinant Dipeptidyl peptidase IV enzyme (DPP-IV, available commercially from R & D Systems) in 50 μl of the assay

buffer (25 mM Tris, pH 7.4, 140 mM NaCl, 10 mM KCl, 1% BSA) to 96 well black flat bottom microtiter plates. The reaction was initiated by adding 50 μ l of 100 μ M substrate Gly-Pro-AMC. The incubation was carried out in the kinetic mode at 30°C for 30 minutes. Fluorescence was measured using Fluorostar at excitation filter of 380 nm and emission filter of 460 nm) Test compounds and solvent controls were added as 1 μ l additions. A standard curve of free amino methyl coumarin (AMC) was generated using 0-100 μ M AMC in the assay buffer. The curve generated, which was linear was used for the interpolation of catalytic activity.

TESTS FOR IC₅₀ STUDIES: Test compounds dissolved in DMSO at 5-6 concentrations were tested in duplicate along with the solvent control and blank samples. Percent inhibition was calculated at each concentration with respect to the solvent control sample (no test compound added). IC₅₀ values were calculated from 3 experiments using the prism software.

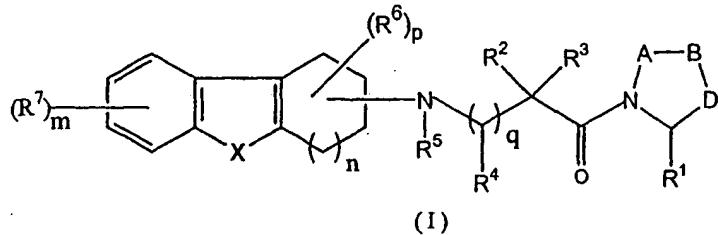
COMPOUNDS	IC ₅₀
Example -1	77.38/67.87 nM
Example - 2	59.19 nM
Example - 3	73.03 nM
Example -4	57% at 300 nM
Example -5	9% at 300 nM
Example -6	1% at 300 nM
Example -7	63.54 nM
Example -8	64.56 nM
Example -9	41.64 nM
Example -10	30% at 300 nM
Example -11	69% at 300 nM
Example -12	13% at 300 nM
Example -13	162 nM
Example -14	7% at 300 nM
Example -15	47% at 300 nM

Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

All patent and non-patent publications cited in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All these publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and 5 individually indicated to be incorporated herein by reference.

CLAIMS

1. A compound of general Formula (I)



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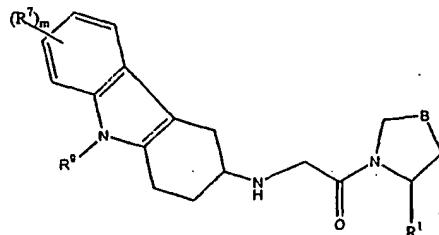
wherein the ring formed by A, B, D, N and the carbon atom to which they are attached is saturated; or optionally contains one double bond; A, B and D may be same or different and are independently selected from the group consisting of CH_2 , CH , S , SO , SO_2 , O , NH , N , N-Z , C=O , CF_2 , CF , C-Z and CH-Z ; wherein Z is chosen independently for each occurrence from the group consisting of hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy and cyano;

wherein R^1 is selected from the group consisting of hydrogen and cyano; R^2 , R^3 and R^4 may be same or different and are independently selected for each occurrence from the group consisting of hydrogen, nitro, hydroxy, cyano, oxo ($=\text{O}$), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, $-\text{S}(\text{O})_r\text{R}^8$, $-\text{S}(\text{O})_r\text{NR}^8\text{R}^8$, $-\text{OR}^8$, and $-\text{SR}^8$; R^8 is selected independently for each occurrence from the group consisting of hydrogen, nitro, hydroxy, cyano, oxo ($=\text{O}$), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic

ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, R² and R³ taken together form oxo (=O); R² and R³ taken together form (=S); R² and R³ together with carbon atom to which both R² and R³ are attached to form a (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R² and R⁴ together with carbon atom to which both R² and R⁴ are attached form (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R⁵ represents hydrogen or substituted or unsubstituted alkyl; R⁶ and R⁷ may be same or different and are independently selected from the groups consisting of hydrogen, formyl, nitro, hydroxy, cyano, oxo (=O), acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ or when two R⁷ substituents are ortho to each other, may be joined to a form a saturated or unsaturated substituted or unsubstituted cyclic ring, which may optionally include up to two heteroatoms selected from O, NR⁹ or S(O)_r; X is oxygen, S(O), or NR⁹; wherein r is 0 – 2; R⁹ represents hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ and protecting groups, wherein m is 0 – 4; wherein n is 0 – 3; wherein p is 0 – 11; wherein q is 0 – 5; or the analogs, tautomeric forms, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein the substituents in the 'substituted alkyl', 'substituted alkoxy' 'substituted alkenyl' 'substituted alkynyl' 'substituted cycloalkyl' 'substituted cycloalkylalkyl' 'substituted cyclocalkenyl' 'substituted arylalkyl' 'substituted aryl' 'substituted heterocyclic ring', 'substituted heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted heterocyclalkyl ring', 'substituted amino', 'substituted alkoxy carbonyl', 'substituted cyclic ring' 'substituted alkylcarbonyl', 'substituted alkylcarbonyloxy' and 'substituted carboxylic acid' may be the same or different with one or more selected from the group consisting of hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), or optionally substituted groups selected from alkyl, 10 alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heteroarylalkyl, heterocyclic ring, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^xR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y$, $-NR^xC(S)R^y$, $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$, $-SO_2NR^xR^y$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yR^z$, $-R^xR^yR^z$, $-R^xCF_3$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, and $-ONO_2$, wherein R^x , R^y and R^z are independently selected for each occurrence from the group consisting of hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroaryl and substituted or unsubstituted heteroarylalkyl.

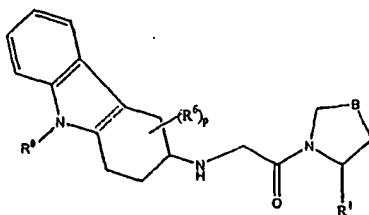
3. A compound according to claim 1, of the Formula I a



(Ia)

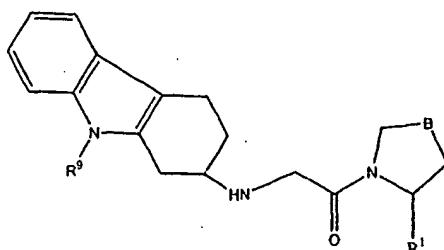
25 4. A compound according to claim 3, wherein m is 0.
 5. A compound according to claim 3 or 4, wherein B is $-S(O)_r$, and r = 0.
 6. A compound according to claim 3-4 or 5, wherein R^1 is hydrogen.
 7. A compound according to claim 3, wherein m is 1.

8. A compound according to claim 3 or 7, wherein B is $-\text{CH}_2-$.
9. A compound according to claim 3, 7 or 8 wherein R^7 is $-\text{OR}^8$.
10. A compound according to claim 9, wherein R^8 is methyl.
11. A compound according to claim 3, 7 or 8 wherein R^7 is halogen.
- 5 12. A compound according to claim 11, wherein the said halogen is selected from the group consisting of Cl and F.
13. A compound according to claim 3, 7 or 8 where in R^7 is ethyl.
14. A compound according to claim 8 wherein R^7 is phenyl.
15. A compound according to claim 7-13 or 14 wherein R^1 is $-\text{CN}$.
- 10 16. A compound according to claim 1-13 or 14 wherein R^9 is hydrogen.
17. A compound according to claim 1-13 or 14 wherein R^9 is methyl.
18. A compound according to claim 1, of the Formula I b.



(Ib)

- 15 19. A compound according to claim 18, wherein p is 1 or 2.
20. A compound according to claim 18 or 19 wherein R^1 is $-\text{CN}$.
21. A compound according to claim 18-19 or 20, wherein B is $-\text{CH}_2-$.
22. A compound according to claim 18-20 or 21 wherein R^6 is methyl.
23. A compound according to claim 18-20 or 21 wherein R^6 is $-\text{CH}_2\text{OH}$.
- 20 24. A compound according to claim 18-22 or 23 wherein R^9 is hydrogen.
25. A compound according to claim 18-22 or 23 wherein R^9 is methyl.
26. A compound according to claim 1,of the Formula I c.



(Ic)

- 25 27. A compound according to claim 26 wherein R^1 is $-\text{CN}$.

28. A compound according to claim 26 or 27, wherein B is $-\text{CH}_2-$.
29. A compound according to claim 26-27 or 28 wherein R^9 is hydrogen.
30. A compound according to claim 1, 1-[2-(8-Methoxy,2,3,4,9-Tetrahydro-*1H*-3-carbazolylamino)acetyl]pyrrolidine-2(*S*) carbonitrile or a pharmaceutically acceptable salt thereof.
- 5 31. A compound according to claim 1, 1-{2-[(3*R*)2,3,4,9-Tetrahydro-*1H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
- 10 32. A compound according to claim 1, 1-{2-[(3*S*)2,3,4,9-Tetrahydro-*1H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
- 15 33. A compound according to claim 1, 1-{2-[(2*RS*)-2,3,4,9-Tetrahydro-1*H*-2-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
34. A compound according to claim 1, 1-{2-[(3*RS*)-3-Hydroxymethyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}-pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
- 20 35. A compound according to claim 1, 1,2-[(3*R*)-2,3,4,9-Tetrahydro-1*H*-3-carbazolylamino]-1-(1,3-thiazolan-3-yl)-1-ethanone or a pharmaceutically acceptable salt thereof.
36. A compound according to claim 1, 1-{2-[(3*R*)-9-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
- 25 37. A compound according to claim 1, 1-{2-[(3*RS*)-3-Methyl-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
38. A compound according to claim 1, 1-{2-[(3*RS*)-6-Fluoro-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl}pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.
- 30 39. A compound according to claim 1, 1-{2-[(3*RS*)-6-Methoxy-2,3,4,9-tetrahydro-1*H*-3-carbazolylamino]acetyl} pyrrolidine-2(*S*)-carbonitrile or a pharmaceutically acceptable salt thereof.

40. A compound according to claim 1, 1-{2-[(3RS)-8-Ethyl-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile or a pharmaceutically acceptable salt thereof.

41. A compound according to claim 1, 1-{2-[(3RS)-4,4,9-Trimethyl-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}-pyrrolidine-2(S)-carbonitrile or a pharmaceutically acceptable salt thereof.

42. A compound according to claim 1, 1-{2-[(3RS)-8-Chloro-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile or a pharmaceutically acceptable salt thereof.

43. A compound according to claim 1, 1-{2-[(3RS)-6-Chloro-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile or a pharmaceutically acceptable salt thereof.

44. A compound according to claim 1, 1-{2-[(3RS)-8-Phenyl-2,3,4,9-tetrahydro-1H-3-carbazolylamino]acetyl}pyrrolidine-2(S)-carbonitrile or a pharmaceutically acceptable salt thereof.

45. A pharmaceutical composition useful as a therapeutically active substance comprising, as an active ingredient, a compound according to any one of claims 1-43 or 44.

46. A pharmaceutical composition useful in the treatment and/or prophylaxis of diseases, which are associated with DPP-IV, the composition comprising, as an active ingredient, a compound according to claims 1-43 or 44, or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

47. A method for the treatment and/or prophylaxis of diseases which are associated with DPP-IV, selected from the group consisting of diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, inflammatory bowel disease, ulcerative colitis, Crohns disease, obesity, and metabolic syndrome, which method comprises administering to a host suffering there from a therapeutically effective amount of a compound according to claims 1-43 or 44.

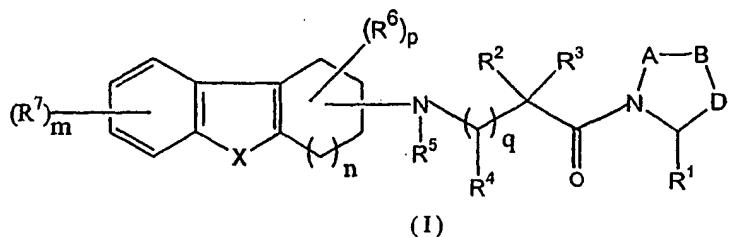
48. A method of treating insulin resistant non-impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus comprising administering to a host suffering there from a therapeutically effective amount of a compound according to claims 1-43 or 44.

49. The method of claim 47 wherein the compound is administered in admixture with a pharmaceutically acceptable excipient, diluent, or carrier.

50. A pharmaceutical composition comprising, as an active ingredient, a compound according to claims 1-43 or 44 or a pharmaceutically acceptable salt or prodrug or hydrate thereof together with a pharmaceutically acceptable carrier or diluent.

51. A method for the manufacture of a medicament or a pharmaceutical composition comprising admixing a compound according to claims 1-43 or 44, and a pharmaceutically acceptable carrier or excipient.

52. A process for the preparation of compounds of the general formula I:



10 wherein the ring formed by A, B, D, N and the carbon atom to which they are attached is saturated; or optionally contains one double bond; A, B and D may be same or different and are independently selected from the groups consisting of CH₂, CH, S, SO, SO₂, O, NH, N-Z, C=O, CF₂, CF, C-Z and CH-Y; wherein Z is chosen independently for each occurrence from the group consisting of hydrogen, halogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy or cyano;

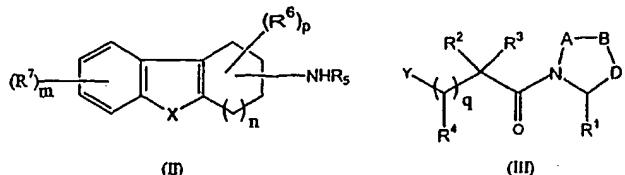
15 wherein R¹ represents hydrogen or cyano; R², R³ and R⁴ may be same or different and are independently selected for each occurrence from the groups consisting of hydrogen, nitro, hydroxy, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, 20 substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, and -SR⁸; R⁸ is selected independently for each occurrence from the group consisting of hydrogen, nitro, hydroxy, cyano, oxo (=O), formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or 25

unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, R² and R³ taken together form oxo (=O); R² and R³ taken together form (=S); R² and R³ together with carbon atom to which both R² and R³ are attached to form a (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) optionally substituted heterocyclic ring; R² and R⁴ together with carbon atom to which both R² and R⁴ are attached form (C₃₋₈) optionally substituted cycloalkyl or (C₃₋₈) 5 optionally substituted heterocyclic ring; R⁵ represents hydrogen or substituted or unsubstituted alkyl; R⁶ and R⁷ may be same or different and are independently selected from the groups consisting of hydrogen, formyl, nitro, hydroxy, cyano, oxo (=O), acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ 10 or when two R⁷ substituents are ortho to each other, may be joined to a form a saturated or unsaturated substituted or unsubstituted cyclic ring, which may optionally include up to two heteroatoms selected from O, NR⁹ or S(O)_r; X is oxygen, S(O)_r or NR⁹; wherein r is 0 – 2; R⁹ represents hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, 15 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ 20 or when two R⁷ substituents are ortho to each other, may be joined to a form a saturated or unsaturated substituted or unsubstituted cyclic ring, which may optionally include up to two heteroatoms selected from O, NR⁹ or S(O)_r; X is oxygen, S(O)_r or NR⁹; wherein r is 0 – 2; R⁹ represents hydrogen, nitro, hydroxy, cyano, formyl, acetyl, halogen, substituted or unsubstituted amino, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, 25 substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylakyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted carboxylic acid derivatives, -S(O)_r-R⁸, -S(O)_r-NR⁸R⁸, -OR⁸, -SR⁸ 30 and protecting groups, wherein m is 0 – 4; wherein n is 0 – 3; wherein p is 0 – 11; wherein q is 0 – 5; or the analogs, tautomeric forms, regioisomers, stereoisomers,

enantiomers, diastereomers, polymorphs, solvates, N-oxides, or pharmaceutically acceptable salts thereof

which comprises the steps of:

(a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of formula (II):



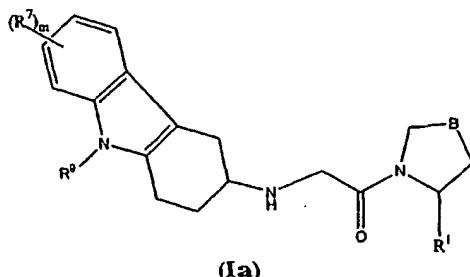
wherein Y is a leaving group, in an inert solvent in the presence of a base.

(b) said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;

10 (c) said coupling occurring for between about 2 hrs to about 7 days; and

(d) isolating the resulting compound of the formula (I).

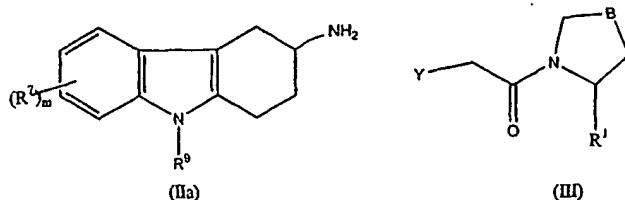
53. A process for the preparation of compounds of the general formula Ia:



15 wherein R^1, R^7, R^9, m are the same as described above in the general formula I and B is selected from the group S or $-CH_2-$;
which comprises the steps of:

which comprises the steps of:

(a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of formula (IIa):

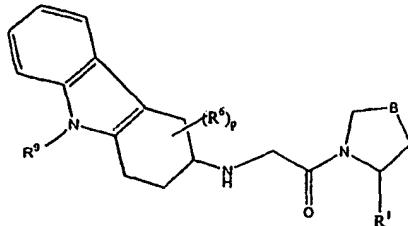


20

wherein Y is a leaving group, in an inert solvent in the presence of a base.

- (b)said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;
- (c) said coupling occurring for between about 2 hrs to about 7 days; and
- (d) isolating the resulting compound of the formula (Ia).

5 54. A process for the preparation of compounds of the general formula Ib:

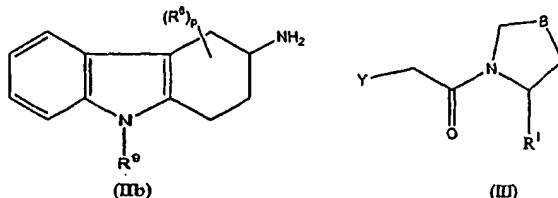


(Ib)

wherein $\text{R}^1, \text{R}^6, \text{R}^9, \text{p}$ are the same as described above in the general formula I and B is $-\text{CH}_2-$ group;

which comprises the steps of:

- (a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of formula (IIIb):



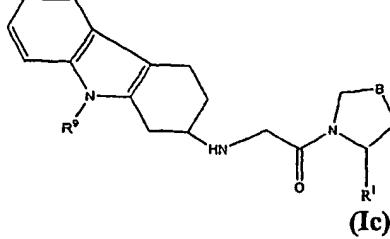
15

wherein Y is a leaving group, in an inert solvent in the presence of a base

- (b)said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;
- (c) said coupling occurring for between about 2 hrs to about 7 days; and

20 (d) isolating the resulting compound of the formula (Ib).

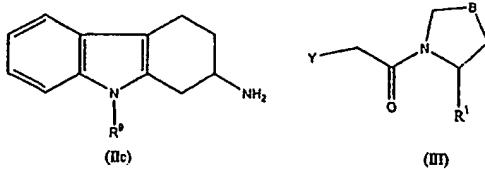
55. A process for the preparation of compounds of the general formula Ic:



wherein R¹,R⁹,p are the same as described above in the general formula I and B is -CH₂- group;

which comprises the step of:

5 (a) coupling one equivalent of a compound of formula (III) with between 1 to 5 equivalents of an amine compound of formula (Ic):



wherein Y is a leaving group, in an inert solvent in the presence of a base.

(b) said coupling occurring at a temperature ranging from about -15°C to about 110°C in an inert solvent such as tetrahydrofuran, dimethyl formamide or dichloromethane;

(c) said coupling occurring for between about 2 hrs to about 7 days; and

(d) isolating the resulting compound of the formula (Ic).

56. The process according to claim 52-54 or 55, wherein said coupling is performed at a temperature of about -15°C to about 110°C.

15 57. The process according to claim 56 wherein said coupling is performed from about 2 hours to about 7 days.

R^xOR^y , $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, wherein R^x , R^y and R^z are independently selected for each occurrence from the group consisting of hydrogen atom, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heteroarylalkyl.

5. 59. The process according to claim 52-54 or 55, wherein Y is a leaving group selected from the group consisting of bromine, chlorine, iodine, O-toulene sulphonyls and O-10 methyl sulphonyls.

60. The process according to claim 52-54 or 55, wherein said inert solvent is selected from the group consisting of tetrahydrofuran, dimethylformamide and dichloromethane.

61. The process according to claim 52-54 or 55, wherein said base is selected from 15 the group consisting of tertiary amines, carbonates and hydroxides.